Pramipexole Approved for Restless Legs Syndrome

Dopamine agonists were already considered first-line treatment.

BY ELIZABETH MECHCATIE
Senior Writer

While misdiagnosis of restless legs syndrome remains common, the Food and Drug Administration has increased the agents available to treat this movement disorder by approving the dopamine agonist pramipexole for moderate to severe cases.

Pramipexole is the second drug and the second dopamine agonist to be approved for this condition. The first was ropinirole (Requip), another dopamine agonist approved last year for restless legs syndrome (RLS), which affects as many as 3% of the population.

Dopamine agonists have been considered first-line treatments for RLS by expert consensus panels before they were approved, according to Dr. John Winkelman, who is medical director of the sleep health center at Brigham and Women's Hospital, and Harvard Medical School in Boston.

Although it will take more time for recognition of RLS to improve, "the good news is that the treatments are so effective and generally so well tolerated, it is very gratifying to treat," and treatment typically produces a rapid response, Dr. Winkelman said.

In his experience, it is "the unusual patient who does not have some response to one of the dopamine agonists, and you need to go back and reassess the diagnosis" in patients who have no response.

Both pramipexole, marketed as Mirapex by Boehringer Ingelheim, and ropinirole, marketed as Requip, have been available for almost 10 years, since they were approved for Parkinson's disease. (Dr. Winkelman is a consultant to Boehringer Ingelheim and to ropinirole manufacturer GlaxoSmithKline, as well as other companies that manufacture products for insomnia and other sleep disorders.)

Pramipexole was significantly more effective than placebo in four randomized, double-blind, 3- to 12-week studies of about 1,000 patients with moderate to severe RLS, which evaluated the effect of treatment on a scale based on patient-reported symptoms and a Clinical Global Impressions scale.

Dr. Winkelman was the lead author of one study of 344 patients, published in September, which found that at 12 weeks, the patients on three fixed doses of pramipexole had significantly greater improvements from baseline than those on placebo in a scale that represented patient rating of symptom severity, which covers different aspects of RLS, such as effects on sleep and next-day functioning.

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In addition, 70%-75% of patients on the three doses of pramipexole studied were rated as "very much improved" or "much improved" on a clinician rating scale, compared with 51% of those on placebo, a significant difference (Neurology 2006;67:1034-9). A strong placebo effect was seen on both of these primary end points, which Dr. Winkelman noted was true for disorders in which people are asked how they are doing.

Side effects were generally mild, with no serious adverse events considered drug-related, Dr. Winkelman said. Nausea was the main side effect that was more common in patients on the drug (19% vs. almost 5%) but was mild and transient.

Because this was a forced titration study, in which patients were titrated up to the preassigned dose even if they responded to a lower dose, side effects may have been more common than if the doses were individualized, he said.

Interestingly, a benefit of the low dose of 0.125 mg over placebo was seen at 1 week, he pointed out.

Restless legs syndrome becomes more prevalent as people age, with the typical age of onset in the 40s and 50s. The symptoms and effects of the disorder are not well recognized, he said, noting that RLS substantially interferes with a person's ability to fall asleep and stay asleep, and with their daytime functioning. People with moderate to severe RLS have symptoms "more often than not"—at least three times a week.

The indications section of the revised label for pramipexole lists diagnostic criteria for restless legs syndrome, including an urge to move the legs that is "usually accompanied or caused by uncomfortable and unpleasant leg sensations," symptoms that begin or worsen during periods of inactivity, such as lying or sitting; and symptoms that are partially or totally relieved by movement such as walking or stretching, for at least as long as the activity continues.

"Why a dopamine agonist works in restless legs syndrome is not entirely clear," he said. Dopamine is involved in the regulation of movement, and potentially in sensorimotor integration, and RLS is considered a sensorimotor disorder.

The dopamine agonist doses used for RLS are much lower than doses used to treat Parkinson's. The FDA-recommended starting dose is 0.125 mg taken once daily 2-3 hours before bedtime. If necessary, the dose can be increased every 4-7 days to 0.25 mg daily, and if necessary, to 0.5 mg daily after another 4-7 days.

The revised label says that there is no evidence that a daily dose of 0.75 mg provides any more benefit than the 0.5-mg dose. ■

Violent Video Games Alter Brain Functioning in Imaging Study

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Adolescents who play violent video games demonstrate distinct alterations in brain activation on functional magnetic resonance imaging, investigators have shown for the first time.

In a study of 44 healthy adolescents, the teenagers who played violent video games demonstrated less activation in the frontal lobes associated with inhibition, concentration, and self-control, and more activation in the amygdala, which governs emotional arousal, Dr. Vincent Mathews reported at the annual meeting of the Radiological Society of North America.

Additional research is needed to determine if this combination of effects could make these individuals more likely to engage in violent behavior. But for now, the study provides parents, physicians, and scientists with data proving that differences in brain function exist in teens who play violent video games, compared with those who don't.

"The fact [that] we are seeing something should at least alert people to the fact [that] something is going on, and that they should be concerned with the types and amount of media they and their children are exposed to," said Dr. Mathews in an interview.

He and his colleagues at Indiana University, Indianapolis, randomly assigned the adolescents to play either "Medal of Honor," a violent video game, or "Need for Speed," an equally exciting but nonviolent game, for 30 minutes immediately before imaging.

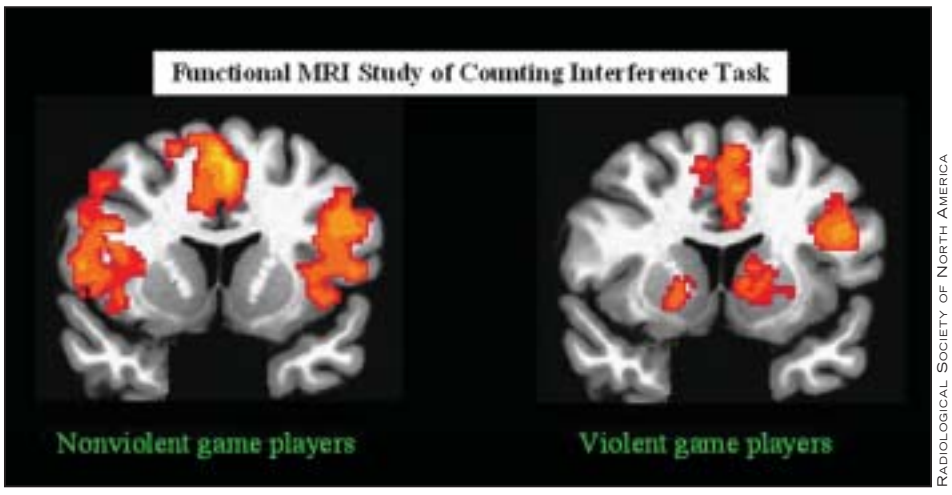
Functional MRI data were acquired on a 3-Tesla scanner using a 2D gradient echo-planar imaging sequence during two modified Stroop paradigms.

In the emotional Stroop task, participants pressed different buttons according to the color of the visually presented words. Words indicating violent actions such as "hit" or "harm" were interspersed with nonviolent action words such as "run" or "walk."

In the counting Stroop task, participants were required to press buttons to indicate the number of displayed objects, with X's used as control events and numerals presented as activation stimulation, Dr. Mathews said.

There was no difference between groups in age, gender, IQ, video playing expertise, or overall violent media exposure. Their mean age was 15 years, and the average IQ was 110 in the nonviolent game group and 108 in the violent game group.

There was no significant difference between groups in accuracy or reaction time during the tasks.



RADIOLOGICAL SOCIETY OF NORTH AMERICA

Functional MRI findings show less brain activation in the frontal lobes and more activation in the amygdala in teens playing violent versus nonviolent video games.

The group that played the nonviolent game showed more activation in the frontal lobes, including the anterior cingulate and dorsolateral prefrontal cortex, during both Stroop tasks, reported Dr. Mathews, professor of radiology at the university.

The group that played the violent game demonstrated less activation in prefrontal lobes during both tasks and increased activation in the right amygdala during the emotional Stroop task. These differences remained after controlling for previous violent media exposure and gender, he said.

There have been numerous studies since the 1970s demonstrating that adolescents exposed to violent media demonstrate aggressive behavior. But because the adolescents in this study were randomized into two similar groups, the findings go more directly to the question of causation than did previous research, Dr. Mathews said.

"There is a little bit more credence to [physicians] recommending limiting this activity," he said, adding that further study is needed to examine behavior and duration of effect in adolescents who watch violent videos. ■